REMARKS

Claims 3, 4 and 11 remain pending in the case.

DRAWING OBJECTIONS

Applicant will submit corrected drawings under separate cover.

REJECTION UNDER 35 USC § 112, FIRST PARAGRAPH

The Examiner has newly rejected the claims for allegedly being supported by a non-enabling disclosure on two separate theories. Claim 3 has been rejected on the basis of the language "greater than 95% sequence identity." Claims, 3, 4 and 11 have been rejected on the basis that the specification fails to enable the use of the claimed nucleic acid for the treatment of cancer. Each ground is addressed separately below.

Relevant law of enablement

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Furthermore, under Patent Office practice, a patent specification is considered to be in compliance with the enabling requirement of § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein. Thus, the Examiner carries the initial burden to substantiate a rejection for lack of enablement. In *re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971). In accordance with the burden, the Patent Office must explain why the truth or accuracy of any statement in the specification is doubted and "back up assertions of its

own with acceptable evidence or reasoning which is inconsistent with the contested statement." Id.; see also, *In re Richard Sichert*, 566 F2.d 1154, 1161 (CCPA 1977)) ("The PTO has cited to no evidence or reference that contradicts or is inconsistent with any supporting statement of the disclosure.").

a) The specification enables nucleic acid with greater than 95% sequence identity with SEQ ID NO:5.

The Examiner states that claim 3 lacks enablement because the specification allegedly fails to enable tumor suppressor molecules that have greater than 95% sequence identity with SEQ ID NO:5. The Examiner admits that one of skill in the art could theoretically produce such molecules, but argues that "it would be burdensome to one of skill in the art to produce all these possible combinations and thereafter determine their activity." Paper No. 25, page 5. The Examiner attempts to support this argument by citing to Lazar et al. (Molec. and Cell Biol. 8(3):1247-1252 (1988)).

It is respectfully submitted that the Examiner has failed to state a *prima facie* rejection for lack of enablement. First, the rejection is deficient in failing to address most of the Wands factors. Second, a proper review of the Wands factors and application of an appropriate standard demonstrates enablement of claim 3 (rather than the contrary).

Nature of the Invention

The claim at issue is directed to a tumor suppressor nucleic acid comprising a nucleic acid sequence that has greater than 95% sequence identity with SEQ ID NO:5. The compounds are identified by a clear functional activity, that being tumor suppression.

State of the Prior Art

The art of tumor suppressor molecules is extensive, as exemplified by the Examiner's own reference for p53 (Malkin et al.), which the Examiner argues covers two decades of research. Although the particular tumor suppressor molecules discovered by Applicant are not

disclosed in the prior art, methods for evaluating and demonstrating tumor suppression are generally applicable and commonly known.

Level of one of Ordinary Skill

Applicant respectfully submits that the level of skill in the art of tumor suppressor molecules and nucleic acid mutagenesis is clearly high. The Malkin reference, which the Examiner admits covers two decades of research for just one tumor suppressor (p53), evidences a high level of skill in the art. Other tumor suppressor genes are also well known and include the retinoblastoma gene, RIZ, fragile histidine triad (FHIT) gene, maspin, BRCA-1, to name just a few. The Examiner, in contrast, has offered no evidence on this Wands factor.

Predictability in the Art

Applicant respectfully submits that the art in the relevant field is reasonably predictable. The Examiner cites to Lazar et al as evidence of alleged unpredictability. The reference, however, supports otherwise. Lazar analyzed amino acid substitutions at two adjoining positions (47 and 48) in TGFα which are highly conserved with the EGF family. P1251, left column. According to Lazar et al., the two amino acid positions showed very different sensitivities to mutation, a finding that Lazar et al. characterized as "unexpected." *Id.* A claim of unexpected results, however, supports that predictability is the norm. Furthermore, many of Lazar's mutants have biological activity, albeit at levels below that of the wildtype protein. Considering the objective evidence of record in its entirety, Applicant respectfully submits that Lazar et al. is not determinative of enablement of Applicant's compositions and that the skilled artisan would acknowledge that it would be predictable to mutagenize less than 5% of positions in SEQ ID NO:5 and that the great majority of such molecules would exhibit tumor suppressor activity.

That Applicant does not indicate where in the molecule mutation is likely to be associated with tumor suppressor activity does not in any way diminish enablement. Methods of mutagenesis and the ease of conducting *in vitro* tumor suppressor activity assays supports that the amount of experimentation is not undue. In fact, because of redundancy of the genetic code, many of the nucleotide sequences that fall within the claim would have the same amino acid

sequence as HTS1. The Examiner's position that the number of possible sequences that need testing is "infinite" is without factual basis.

The Amount of Direction or Guidance Present

Contrary to the Examiner's assertion, the specification provides extensive guidance on how to prepare the claimed tumor suppressor nucleic acids and to verify tumor suppressor activity. The specification provides the full nucleotide sequence in the form of SEQ ID NO: 5, which encodes a novel human tumor suppressor protein. The specification describes vectors for cloning and expressing the tumor suppressor protein from the nucleic acid. Methods of mutagenesis are well known in the art. The specification teaches proliferative assays with cells such as mammalian cells lines, yeast cells, insect cells and amphibian cells to evaluate the activity of the claimed tumor suppressor. (See page 35 lines 1-10) Example II demonstrates the use of a soft agar colony assay to evaluate suppression by the tumor suppressor nucleic acid, while assays for anchorage independent growth are shown in Examples V and VI. It is noted that the specification describes an array of tumor assays which are in common use in the tumor suppressor gene field. The Examiner, in contrast, has offered no evidence on this Wands factor.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge that the specification provides extensive guidance for making the claimed compounds and for selecting those with the appropriate activity.

Presence of Working Examples

As already mentioned, the working examples of the specification provide further enabling support for compound selection methods. Example III describes isolation and characterization of the HTS1 nucleic acid, Example IV demonstrates expression of the suppressor gene in HeLa and HF cells, while Example VI demonstrates that HTS1 nucleic acid overexpressed in HeLa cells results in tumor suppression. The Examiner, in contrast, has offered no evidence on this Wands factor.

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that the working examples of the application support enablement of the claims at issue.

Quantitation of Experimentation Necessary

Applicants respectfully submit that the amount of experimentation necessary is not undue. The nucleic acid sequence is described, methods of mutation are well known, and the application and the field as a whole provide an array of assay formats to evaluate nucleotide sequences which vary by less than 5% yet retain tumor suppressor activity. The situation is similar to that in In re Wands (8 USPQ2d 1400), where hundreds of hybridomas were screened to identify only a few high affinity IgM antibodies.

Claim 3 Meets the Enablement Standard of 35 U.S.C. §112, first paragraph.

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Applicant respectfully submits that claim 3 meets the enablement standard of 35 U.S.C. § 112, first paragraph. The Examiner's opinion to the contrary is not founded on a proper Wands analysis. Because the enablement requirement of 35 U.S.C. § 112, first paragraph, has been met, Applicant respectfully requests that the rejection be reconsidered and withdrawn with respect to Claim 3.

b) The alleged failure to enable treatment of cancer with the claimed tumor suppressor nucleic acid is without basis in law or fact

1. No law supports the Examiner's Requirement

A basis for lack of enablement of claims 3, 4 and 11 is the alleged failure to enable treatment of cancer with the claimed tumor suppressor nucleic acid. The Examiner acknowledges that the claims are directed to a composition, and that the specification enables use of the composition for diagnostic purposes. Nevertheless, it is the Examiner's position that the specification must enable all intended uses of the composition including treatment of cancer because the claims are given "the broadest interpretation."

It is respectfully submitted that giving claims their broadest interpretation has nothing to do with a requirement that a specification enable all possible uses of a composition for the composition to be enabled. A patent specification must teach how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (copy attached). This clearly means that one must teach how to make all the compounds that reasonably could fall within the scope of the claim. One must also describe a statutory utility for all such compounds and support such utility with an enabling disclosure. However, there is no requirement that a patent describe all possible uses of a composition, let alone a requirement that a specification enable all uses, when a composition claim is at issue. Implementation of such a rule would lead to the absurd result that an otherwise fully enabled composition claim becomes non-enabled merely by the inclusion of additional (non-required) speculative uses (a situation not present in the instant application).

Applicant has found no law, regulation or rule to support this position. Giving a composition claim its broadest reasonable interpretation is to examine whether all the compounds falling within the claim can be made and used in accordance with the invention. This was precisely the analysis in *In re Wright*, where a narrow scope of compounds was deemed enabled but not the broader scope of compounds. As there is no requirement to have more than one utility for a novel composition, it stands to reason that any enabled utility meets that requirements of 35 U.S.C. § 112, first paragraph.

Applicant respectfully requests that the Examiner cite to some legal authority which clearly supports this requirement or withdraw the rejection.

2. The specification is enabling in any event

It is respectfully submitted that the Examiner is incorrect that the specification does not enable claims 3, 4 and 11. The specification recites and enables numerous uses of the claimed composition including the treatment of cancer.

i) Diagnosis of cancer using the claimed nucleic acids

The specification teaches that SEQ ID NO:5 or a functional fragment thereof can be used to hybridize to this nucleic acid under moderately stringent conditions. See p25, lines 11-17. The specification also teaches that one can make antibodies to the HTS1 tumor suppressor protein encoded by SEQ ID NO:5. See p32, line 32 to page 33, line 24. Tumor suppressor protein can be obtained by isolating, cloning and expressing the claimed nucleic acids as described in the application. See p29, lines 3-21.

The specification teaches a method of detecting a neoplastic cell in a sample using the HTS1 tumor suppressor nucleic acid of the invention or antibodies to the protein encoded thereby. See p41, lines 1-14. Altered expression or structure of the tumor suppressor is described using nucleic acid hybridization or binding to a detectable agent such as an antibody. In the case of hybridization, the specification describes various methods including *in situ* hybridization for altered chromosomal location, northern blotting, and RNase protection for RNA, Southern blots for copy number and integrity, and detection of single base mutations using RTPCR and PCR. See p41, line 24 to page 42, line 5. Methods to detect altered expression of the HTS1 polypeptide are also extensively described. See p42, line 15 to page 43, line 2.

ii) Therapy of cancer using the claimed nucleic acids

The specification describes appropriate assays to determine that the nucleic acids of the invention alter cell proliferation to so as to restore normal proliferative characteristics to a cancer cell. See p35, line 1 to page 36, line 10. As already discussed, Examples IV and V teach expression of the HTS1 nucleic acid in human cells and detection of anchorage independent growth, and Example VI demonstrates that an expression vector encoding HTS1, which results in overexpression of HTS1 in HeLa cells (a human cervical cancer cell), results in reduced proliferative activity as measured in the soft agar colony assay.

The specification also teaches various vectors that can be used to deliver the claimed tumor suppressor nucleic acid in vivo. See page 36, line 12 to page 37, line 25. Methods to deliver the vector such as by transfection, lipofection and the like also are described. See page 36, line 26 to page 37, line 6. Approaches to formulate the claimed nucleic acids for

administration *in vivo* is described along with guidelines for dosing. See page 37, line 8 to page 38, line 21.

The Examiner asserts that there is no nexus between the use of the claimed nucleic acids in *in vitro* cultured cell lines, as a diagnostic tool, and as an *in vivo* therapeutic, and that the specification fails to establish a correlation between *in vitro* assays and effectiveness *in vivo*. However, as already discussed, Applicant has enabled several diagnostic uses of the claimed nucleic acids, any one of which is sufficient to satisfy the enablement requirement for a composition claim.

The Examiner argues that the specification provides insufficient guidance as to which types of tumor cells can be suppressed or the manner at which suppression is accomplished. However, Applicant points out that the specification identifies a variety of cancer cells suitable for treatment (see p41, lines 15-22) and demonstrates suppression of the tumor phenotype in a well known cervical cancer cell line (i.e. HeLa cells; see Example VI). Furthermore, there is no requirement to describe how a claimed method works, although it is clear that the claimed nucleic acids function as tumor suppressors.

The Examiner has not met his/her burden to establish that one skilled in the art would not believe that the specification provides sufficient teaching upon which to use the claimed nucleic acids for cancer therapy. The Examiner resorts to the Malkin reference to support that Applicant's method of treating cancer is not enabled. According to the Examiner, Malkin stands for the proposition that "after two decades of studying the properties of p53, methods of inhibiting tumor progression and initiation by means of p53 are not yet at hand." Quite to the contrary, the Malkin reference demonstrates that clinical utility of the p53 gene is at hand. See Abstract ("The next decade promises to offer exciting opportunities to apply our vast knowledge of this intriguing tumor suppressor to clinical advantage."). That it may have taken two decades for p53 to reach this point, supports enablement of the claimed nucleic acids because gene therapy with the claimed tumor suppressor nucleic acids can take advantage of the development work from p53 that is applicable to any tumor suppressor approach (e.g. the use of a delivery

vehicle). Thus, the Examiner has failed to state a *prima facie* case of non-enablement for using HTS1 nucleic acids in cancer therapy.

In sum, the enablement rejection is entirely without basis in the law as the claimed nucleic acids are enabled for a variety of diagnostic uses. Having satisfied the enablement requirement for composition claims, Applicant need not demonstrate enablement of cancer therapy using the tumor suppressor nucleic acids. Nevertheless, the enabling qualities of the specification in this regard have been amply demonstrated. Accordingly, for all of the above reasons, the Examiner is respectfully requested to reconsider and withdraw the rejection for lack of enablement.

SUMMARY

It is respectfully submitted that the above amendments and remarks place the application in condition for allowance. Accordingly, reconsideration and favorable action on all the claims is respectfully requested. If a telephone call would further prosecution of this case, the Examiner is invited to call the undersigned attorney at (858) 847-6722.

The Commissioner is hereby authorized to charge the fee for the extension of time and any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. The Commissioner is hereby

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authorized to charge any fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this transmittal, or to credit any overpayment, to **Deposit Account No. 50-0872**.

Respectfully submitted,

Date October 17, 2003

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